

The prevalence of potential drug interactions in Intensive Care Units

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Abstract

Aims: Drug interaction occurs when a drug affects the action of another. In this line, the present study has been conducted to determine the prevalence of potential drug interactions in critical care units.

Methods: In the present retrospective study, the first twenty-four hour prescriptions of 371 patients admitted to intensive care unit of Shahid Bahonar hospital of Kerman were investigated in terms of the number and type of drug interaction in addition to other factors such as number of drugs, age, gender, length of ICU stay and number of prescribing doctors. In order to determine the number and type of drug interactions, a reference textbook of "Drug Interaction Facts" was used, and data analysis was performed by SPSS₁₈ statistical software with respect to the study objectives using descriptive statistics, Pierson correlation test, independent t-test, and variance analysis.

Results: In terms of the drugs received, 77 different drugs and, in total, 2091 cases of drug prescription were found with the average of 5.6 (± 1.5) for each patient. Overall, 726 cases of drug interactions were observed among critical care unit patients in the first 24 hour of prescription. Delayed, moderate, and possible interactions were accounted for the most interactions found. The results are indicative of a significant correlation between the number of drug interactions and prescribed medications, age, gender, duration of hospitalizations and number of prescribing doctors.

Conclusion: Due to possessing more risk factors of drug interactions, critical care unit patients are at higher risk of developing drug interaction which behooves the medical team to pay more attention to this issue.

Key words: Intensive Care Unit; Drug interaction; Prevalence

Introduction

Potential drug interaction is a situation in which a drug action is likely to be altered by the concurrent administration of another drugs [1] and can be observed in both pharmacokinetic and pharmacodynamic states. In pharmacokinetic intervention, a drug alters the absorption, distribution, metabolism, and the clearance of another drug, and in pharmacodynamic intervention, the drug specific performance is changed by the other drugs [2]. According to the Medical Association of America, 44 to 98 thousand deaths occur each year as a result of medical errors, seven thousands of which owing to negative side effects of drugs. Almost 6.7 percent of patients admitted to hospital undergo adverse drug complications which bring about 0.34% mortality rate among this group. In 2000 in the United States of America, the fourth rank has been allocated to adverse drug effect-caused mortality after cardiovascular disease, diabetes and AIDS [3]. The risk and severity of drug interactions varies under the influence of factors such as

number of medications received, duration of treatment, patients' age, the number of prescribing physicians and stage of disorder [1, 3].

Critical care unit patients receive more medication compared to the patients in other wards [4] and are therefore more subjected to the risk of drug interactions [1, 2, 4, 5, 6]. In a study by Lima et al. in Brazil, 311 cases of potential drug interactions have been reported in critical care unit patients [5]. In this line, the results of a study by Hammes et al. in 2008 [6] also indicated higher risk for the occurrence of potential drug interactions in intensive care unit patients. Limited studies have been conducted in this field in our country. In an investigation by Hajebi et al. performed in four wards of an educational hospital, 156 cases of drug interaction have been reported [7]. In another study by Nazari et al. (2004) in intensive care unit of one of the teaching hospitals in Tehran, 413 cases of potential drug interactions have been announced [4]. Although all drug interactions are not preventable, medical team's awareness

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on the incidence of potential drug interactions and the risk factors increasing the possibility of drug interaction as well as familiarity with the mechanisms involved in this phenomenon can reduce the real occurrence of drug interactions among the patients hospitalized [5]. In this regard, the present study has been carried out to investigate the prevalence of potential drug interaction and the associated risk factors in critical care units of Shahid Bahonar hospital of Kerman.

Methods

The present retrospective study was undertaken to determine the prevalence of potential drug interactions and related risk factors in intensive care unit patients of Shahid Bahonar hospital of Kerman. To collect the information, medical records of all patients hospitalized in these wards from late March 2009 to late March 2010 were evaluated. The participants only included those who were directly transferred to intensive care units, for whom medical records had been established. The number of drugs received by patients in the first 24 hours of hospitalization in critical care units was extracted from patients' records. Other parameters such as the names of drugs received and their prescription patterns were also collected and recorded in the standard forms. Patients' demographic information including age, gender, marital status, number of physicians, duration of hospitalization in the ward, and mode of discharge were accessed from Medical Record Department of hospital and recorded in information

collecting forms. In order to determine drug interaction for each patient, the reference textbook of "Drug Interaction Facts", published in 2010, was applied [8]. In this book, drugs are arranged based on English alphabet, and type of interactions in terms of initiation (abrupt or delayed), intensity (low, medium and high) and possibility (established, probable, suspect, possible, and implausible) is separately specified for each drug. Those drugs for which the names were not mentioned in the book would be considered as non-interactive. Moreover, nutritional supplements, serums, electrolytes and vitamins have not been investigated. After determination of drug interactions and their mechanisms, data were analyzed by the researchers for all patients in accordance to the study objectives using SPSS₁₈ statistical software by descriptive statistics, Pearson correlation tests, independent t-test and the variance analysis.

Results

From a total of 371 patients studied, with the mean age of 39.8 (± 22.1) years, 75.2% were male and the rest were female. The average number of prescribing physicians was 2.7 for each patient, and the average length of hospitalization in critical care unit was 17.7 (17.4) days. In terms of patients discharge from these wards, 55.3%, 15.6% and 29.1% of participants were respectively discharged following recovery, the ward's follow up, and death among 371 patients admitted. In terms of type of drugs received, 77 different drugs and, in total, 2091 cases of drug prescription

Table1. The list of the ten most consumed drugs in the Critical Care Unit

Drug name	Times of prescription	Drug name	Times of prescription
1. Ranitidine	276	6. Keflin	123
2. Phenytoin	256	7. Midazolam	97
3. Ceftazidime	157	8. Pantoprazole	84
4. Morphine	150	9. Dexamethasone	78
5. Vancomycin	150	10. Ceftriaxone	72

were found with the average of 5.6 (± 1.5) for each patient. Injected drugs (shots) accounted for 1849 number of prescribed medications. With respect to the frequency of drug administration, ranitidine and phenytoin were the most consumed drugs with 276 and 256 times prescription (Table 1).

Overall, 726 cases of drug interactions were observed among critical care unit patients in the first 24 hours of prescription. In terms of initiation, intensity and possibility of drug interactions, delayed, moderate and probable types accounted for the largest percentage of drug interactions respectively. From the total of 726 cases of drug interaction found, 25 were major interactions, eight of which was related to ranitidine-phenytoin interaction and seven cases to phenytoin-dopamine. The greatest number of drug interactions has also been observed between ranitidine and phenytoin with 213 cases. The results obtained by the Pearson correlation test are indicative of a significant difference between the number of drug interaction and the number of prescribed medications ($p < 0.001$, $r = 0.563$). The test also showed significant relationship between the number of drug interactions with the number of hospitalization days and prescribing physicians ($p < 0.05$, $r = 0.32$). The results of the mentioned test displayed an inverse relationship between the number of drug interactions and patients' age ($p < 0.05$, $r = 0.127$). To determine the correlation between the number of drug interactions and patients' gender, independent t-test was used and findings indicated more interactions in men compared to women ($p < 0.05$). Furthermore, variance analysis represented a meaningful association between the number of drug interactions and patients' mode of discharge, so as drug interactions were higher in patients discharged from recovery (2.15 ± 1.65) than deceased ones (1.73 ± 1.32) and those in need of follow up (1.67 ± 1.32) ($p < 0.05$).

Discussion

Previous studies have demonstrated high possibility of drug interaction in critical care

unit patients [1, 2, 4, 5 and 6]. The results of the present study is also well indicative of high risk of drug interaction among patients in intensive care unit as 726 cases of interaction have been found in the first 24 hours of prescription in these wards. In a study by Almeida et al. (2010) on the prevalence of potential drug interactions in critical care units, interaction rate has been reported to be higher in these units compared to the others; on the explanation of this finding, Almeida et al. have stated that due to types of receiving drugs and special clinical status, intensive care unit patients are at high risk of drug interaction [1]. In an investigation by Lima et al. on 102 patients hospitalized in critical care unit, the risk of potential drug interaction has been reported to be high with 311 cases of interactions found [5]. In terms of initiation, intensity and possibility of drug interactions, delayed, moderate and probable types accounted for the largest percentage of drug interactions respectively. In this regard, Hammes et al. study revealed more than 59% cases of delayed type of drug interaction in critical care units as well as higher prevalence of moderate and possible types compared to the others [6]; on the explanation of this phenomenon, it can be stated that since a great percentage of interactions has been between the two most in demand drugs, ranitidine and phenytoin, between which the interaction was of delayed, moderate, and possible types in the present study, allocation of more interactions to delayed, moderate, and possible types seems to be rational. The most common interactions observed were associated to ranitidine and phenytoin, which were also the most consumed drugs in critical care units, as the stomach acid neutralizers and anticonvulsive drugs. Almeida study has similarly pointed to anticonvulsants and stomach acid neutralizers as the most consumed drugs after non-steroidal anti-inflammatory drugs in intensive care units [1]. Approximately 75% to 100% of ICU patients are subject to developing peptic stress ulcers due to clinical problems they are facing, and preventive measures are hence performed for the most patients in risk [9]; stomach acid

neutralizing drugs, such as ranitidine, are currently the top priority to meet this goal [10]. In line with the results obtained by Nazari et al. in Tehran [4] and other investigations [1, 5], the study findings exhibited that the more the number of prescribed drugs for patients is, the more the possibility of drug interaction occurrence will be. More incidence of drug interaction proportional to the increase in the number of drugs received by patients appears to be reasonable. The results of the study also showed that men are at higher risk of drug interactions in critical care units compared to women, and the possibility of interactions have inverse relationship with patients' age. However, Lima et al. study displayed contradictory results, as they indicated higher risk of drug interactions in women and those over 60 years of age in intensive care units, which can be justified by higher percentage of women participated in their study compared to men and higher risk of drug interaction in this group as a result. They also declared that due to numerous and more serious clinical problems in patients over 60 years of age, the possibility of receiving more medications and the consequent occurrence of drug interactions is increased in this age group [5]. As noted, the results of the present study are inconsistent with those obtained by Lima et al.; however, a more in-depth look into the issue shows a relative association between the two studies. According to Lima et al., more prevalence of drug interactions in the elderly goes back to multiple and more severe problems in this age group; if the mentioned problems are the reasons behind higher incidence of drug interactions, more occurrence of interactions among young participants in the present study can be justified by high percentage of trauma patients, who are encountering more serious and numerous problems compared to other patients, admitted to critical care units in the present research on one hand, and high percentage of trauma patients in the young age group compared to the other age classes [11] on the other. More prevalence of drug interactions in women has also been ascribed

by Lima et al. to more percentage of this gender participated in comparison with men; if it is reasonable to attribute more interactions in women to their more participation, the situation was reversed in the present study in which men outnumbered women in terms of participation, contributing to more possibility of interaction occurrence. However, similar to more occurrences of interactions in the young age group, more prevalence of potential drug interaction in males compared to females seems to be mostly owing to the difference in clinical status between the two genders; just as trauma occurrence is more prevalent in young people, severe traumas are 2.5 times higher in men than women [11, 12]; hence, men have been more likely to develop a worsening clinical status in the presents research in comparison with women, justifying more drug prescription and consequently more incidence of drug interactions.

The study results also showed higher possibility of drug interactions in line with increase in the number of prescribing physicians. Likewise, greater number of prescribing doctors has been mentioned by Almeida et al. [1] as one of the reasons for the more occurrence of drug interaction. This finding can be explained by the fact that due to numerous clinical problems in critical care unit patients, they are examined by several clinical specialists, each of whom prescribes different drugs which, per se, contributes to increment in the number of medications received by patients and ultimately more drug interactions. The study results also displayed more hospitalization duration in critical care unit patients with more possibility of drug interaction, which is in consistence with the study by Hammes et al. in 2008 [6].

Since the present investigation has only evaluated the incidence of potential drug interaction in the first 24 hours of hospitalization, it cannot be definitely concluded that whether drug interactions have led to more duration of ICU stay or not; nonetheless, it is likely that patients with more duration of ICU stay have been in more need of examination and treatment for their

dire clinical situation on one side, and have been examined by a large number of physicians on the other, resulting in an increase in the number of medications received and higher incidence of interactions. The relationship between the mode of patients discharge and the possibility of drug interaction has also been assessed for the first time in the present study, and the results are indicative of the more potential drug interactions in patients who have been discharged following recovery than deceased ones and the other patients. Considering patients' serious condition which leads to more medications administration and consequently higher potential drug interactions, and given the more deleterious status of deceased patients compared to the others, a question is raised in this regard that why the number of drug interactions is less in deceased patients than those who have been discharged after recovery or the ward's follow up. A compelling reason to answer the question is that in spite of critical situations of deceased patients, they were most likely to die in the first hours of hospitalization in the ICU and had therefore spent less time in the ward instead of 24 hours (three working shifts) and received less medication, probably once in each shift instead of three times, which eventuated in less medication administration in these patients compared to recovered ones and, thus, lower possibility of drug interactions occurrence in this group. In terms of drug administration in critical care units, injection, with 1841 cases, was determined to be the most common method used in these wards.

Lima et al. have similarly pointed to intravenous injection as the most frequent way of drug administration in their study, which could be owing to more serious clinical condition of these patients, raising the need to more prompt administration of drugs, and intravenous injection as the best possible option for this purpose [5]. Of course, some patients' inability to receive oral medications, receiving a greater volume of drugs through intravenous administration, and allowing drugs to be infused can also be enumerated as

the reasons for intravenous injection as the priority choice in intensive care unit patients [10].

Conclusion

Taken together, it can be concluded that the prevalence of potential drug interaction is high in critical care units and is influenced by factors such as a large number of drugs received by patients, serious and numerous clinical problems, a great number of prescribing physicians, and intravenous route for drug injection. Although all the potential drug interactions do not show up as the actual ones, high prevalence of potential drug interactions can be a warning bell for the incidence of actual drug interactions in critical care unit patients [1]; therefore, it requires medical team to pay further attention to this issue for preventive measures.

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References

1. Almeida S M, Gama C S, Akamine N. Prevalence and classification of drug-drug interactions in intensive care patients. *einstein*. 2007;5(4):347-51.
2. Papadopoulos J, Smithburger P L. Common drug interactions leading to adverse drug events in the intensive care unit: Management and pharmacokinetic considerations. *Crit Care Med*. 2010; 38:126-35.
3. Committee on Quality of Health Care in America: Institute of Medicine. *To err is human: building a safer health system*. Washington, DC: National Academy Press. 2000.
4. Nazari M A, Moghadam N. Evaluation of Pharmacokinetic Drug Interactions in Prescriptions of Intensive Care Unit (ICU) in a Teaching Hospital. *Iranian J Pharmaceutical Res*. 2006;3: 215-18.
5. Lima F E, Cassiani S H. Potential drug interaction in intensive care patients at a teaching hospital. *Rev Latino-am Enfermagem*. 2009;17:222-7.
6. Hammes J A, Pfuetzenreiter F, Silveira F D, Koenig A, Westphal A G. Potential drug interactions prevalence in intensive care units. *Rev Bras Ter Intensiva*. 2008;20:349-54.

7. Hajebi G, Mortazavi SA. An investigation of drug interactions in hospital pharmacy prescriptions. *Iranian J. Pharm Res.* 2002;26(3):205-15.
8. Tatro D S. *Drug Interaction Facts.* St Louis, Walters Kluwer Health. 2010.
9. Marino P L. *The ICU Book.* 3rd ed. New York, Lippincott Williams & Wilkins. 2007:67.
10. Daley R J, Rebeck J A, Welage L S, et al. Prevention of stress ulceration: current trends in critical care. *Crit Care Med.* 2004;32(10):2008-13.
11. Howard P K, Steinman R A. *Emergency Nursing.* 6th ed. St Louis, Mosby. 2010;6:234-6.
12. Iranmanesh S, Rafiei H. Normal saline instillation with suctioning and its effect on oxygen saturation, heart rate, and cardiac rhythm. *J Med Scien & Res.* 2010;4(3):117-20.
13. AhmadiNejad M, Rafiei H. Pressure ulcer incidence in intensive care unit patients in Bahonar Hospital, Kerman. *J Iran Soc Anaesthesiol Intensive Care.* 2011;57:10-6.
14. Rafiei H, Iranmanesh S, Sabzevari S. Comparison of the endotracheal tube suctioning with and without normal saline solution on heart rate and oxygen saturation. *Iranian J Critical Care Nursing.* 2011;4(3):117-20.